REMARKS

Amendments to the Claims

Claims 1-12 and 26-41 are pending in this application. Claims 2-6 are canceled. Claims 1 is amended to further clarify the invention. Claims 7, 8, and 11 are amended to correct claim dependency. Previously withdrawn claims 18-22 are amended to correct claim dependency. Claims 26-41 are new. Support for the amendments can be found throughout the specification as originally filed and specifically on p. 4, ll. 31-33, p. 17, ll. 17-19, p. 18, ll. 1-26 (Table 2), and p. 15, l. 5 – p. 18, l. 26 (Example 2). No new matter has been added to the application as a result of the present amendments.

Rejection of claims 1 and 4 under 35 U.S.C. § 112, second paragraph

Claims 1 and 4 stand rejected under 35 USC § 112, second paragraph, as being indefinite. Specifically, the Office asserts that claim 1 is incomplete for lack of conclusion with regard to the "determining" step (step "d") and lacks specific direction of the performance of the "determining" step (step "d"). The Office further asserts that the phrase "preferably" renders claim 4 indefinite because it is not known which of the preferable three cell lines are required of the claimed invention. Applicants respectfully traverse this rejection.

While Applicants believe the claims were clear, in an effort to further clarify claims 1 and 4 (new claims 29-30), these claims have been amended. Claim 1 has been amended to recite "determining the presence of the one or more steroid ligands in the sample based on effect profiling of the measured activity". The principle of effect profiling based on the activity of the reporter gene measured can be found on p. 15, l. 5 – p. 18, l. 26 (Example 2) of the specification as originally filed. Specifically, steroid ligands are identified based on different responses of the two or more cell lines to the steroid ligand, and present step now (c) directly refers to the measured activity of the reporter gene (step b). Claim 4 (new claims 29-30) has been amended to remove the phrase "preferably".

Applicants believe that for the reasons discussed above, the pending claims are clear and definite. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, second paragraph.

Rejection of claims 1-12 under 35 U.S.C. § 112, first paragraph

Claims 1-12 stand rejected under 35 USC § 112, first paragraph, for failing to comply with the written description requirement. The Office asserts that the claims contain subject matter which

was not described in the specification in such a way as to reasonably convey to one skilled in the art that the applicant at the time the application was filed had possession of the claimed invention.

Applicants respectfully traverse this rejection and submit that the Office has misapprehended and misapplied the written description requirement and case law on relating to it.

The seminal case law relating to written description (which the Written Description Guidelines refer to), *Eli Lilly*, *Enzo Biochem*, and *University of Rochester*, all address written description deficiencies not present in the instant application. Those cases dealt with claims reciting new or unknown biological materials, using functional rather than structural language to describe them, and the issue was whether such language was sufficient for one of ordinary skill in the art to believe the applicant had possession of the claimed subject matter. The present claims do not recite new or unknown biological materials.

In the *University of Rochester* case the applicant had discovered two distinct cyclooxygenases, referred to as "COX-1" and "COX-2" and that it would be advantageous to selectively inhibit COX-2, which would lead to inhibition of prostaglandin synthesis catalyzed by mammalian prostaglandin H synthase-2 (PGHS-2). The applicant sought and obtained claims to methods of inhibiting PGHS-2, which claims required selective COX-2 inhibitors. But the specification disclosed no selective COX-2 inhibitors, only methods of finding them. The court held the claims invalid because they required possession of selective COX-2 inhibitors to use the claimed invention, and no such inhibitors were disclosed or even known. Nor did the application provide sufficient teachings for one of ordinary skill in the art to discern a COX-2 inhibitor without screening, which would involve substantial experimentation without any reasonable assurance of success given that there were no known selective COX-2 inhibitors.

Similarly, in the *Eli Lilly* case, the claims at issue required human insulin cDNA, but the specification did not disclose the human insulin cDNA sequence, it was not unambiguously derivable from the specification, and the sequence of human insulin cDNA was not otherwise known. The court held that the claims were invalid for lacking written description support because the specification did not reasonably apprise those of ordinary skill in the art that the patentees had possession of human insulin cDNA needed to make and use the claimed invention. The sequence was unknown and not unambiguously derivable.

In the *Enzo* case, the claims were directed to a composition reciting, in part, a nucleic acid sequence described functionally as hybridizing to chromosomal DNA of *Neisseria gonorrhoeae*, but the specification disclosed no specific sequences, only the deposit of *Neisseria gonorrhoeae* recombinant DNA within an *E. coli* host. The court held that the claims satisfied the written

description requirement because there was a direct correspondence between the structure of the deposited nucleic acid material (*i.e.*, its sequence) and the function of hybridizing to chromosomal DNA of *Neisseria gonorrhoeae*, which was known through the deposit. Thus, the required sequences were well defined and routinely obtainable, which was in contrast to the situations in *Eli Lilly* (where the required cDNA was not well defined nor routinely an unambiguously obtainable) or *University of Rochester* (where the require COX-2 inhibitors were not well defined, not routinely obtainable, nor even known to exist).

No such issues arise with respect to the present claims. The claims only require cell lines originating from human osteoblastic cell line U2-OS comprising an expression plasmid coding for a different steroid or thyroid hormone receptor or a ligand modifying factor and a reporter gene construct responding to a cellular pathway which is induced by a steroid ligand. These cell lines and expression palsmids contained within are well-known, well-defined biological compounds.

As the Federal Circuit stated in *Amgen Inc. v. Hoechst Marion Roussel Inc.*, 65 USPQ2d 1385, 1398 (Fed. Cir. 2003), "Both *Eli Lilly* and *Enzo Biochem* are inapposite to this case because the claim terms at issue here are not new or unknown biological materials that ordinarily skilled artisans would easily miscomprehend." The situation is the same here.

The Office asserts that the application does not disclose any of the specific cellular ligands or the ligand modifiers of said broadly claimed specific components and that the number of examples provided does not commensurate with the scope and breadth of instant claims. Furthermore, the Office asserts that the disclosure of a single species rarely, if ever, sufficient to describe a broad genus, particularly when the specification fails to describe the features of that genus, even in passing.

Applicants respectfully submit that the Office errs in assuming that a genus must be supported by a representative number of species in the specification. There is no such requirement. The Written Description Guidelines and the case law upon which it is based make clear that a having a representative number of species is merely one way in which the written description requirement for a claimed genus may be satisfied, but it is by no means the only way and certainly not required. For example, it is well settled that a generic claim to a chemical compound comprising a skeleton structure with several substituents that are completely defined (*e.g.*, in Markush fashion) satisfies the written description requirement without any representative species.

When an originally filed application provides an explicit description of a genus, the applicant need not provide additional implicit support. Implicit support, such as through disclosure of a representative number of species or through the disclosure of structure-property or structure-

function relationships, is generally only relevant when explicit support is absent. *See, e.g., In re Robins*, 429 F.2d 452, 456-57, 166 USPQ 552, 555 (CCPA 1970) ("Mention of representative compounds encompassed by generic claim language clearly is not required by Section 112 or any other provision of the statute. But, where no explicit description of a generic invention is to be found in the specification, . . . mention of representative compounds may provide an implicit description upon which to base generic claim language."); *In re Grimme*, 274 F.2d 949, 952, 124 USPQ 499, 501 (CCPA 1960) ("[I]t may not be necessary to enumerate a plurality of species if a genus is sufficiently identified in an application by 'other appropriate language.'").

So, for example,

> In claims involving chemical materials, generic formulae usually indicate with specificity what the generic claims encompass. One skilled in the art can distinguish such formula from others and can identify many of the species that the claims encompass. Accordingly, such a formula is normally an adequate description of the claimed genus.

Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406 (emphasis added).

The applicants also note that the Written Description Guidelines state that the written description requirements "may be satisfied" by a representative number of species, not that a representative number of species "must be" be present.

The present claims recited a genus, which, although large, is completely defined by the known elements comprising it: human osteoblastic cell line U2-OS comprising an expression plasmid coding for a different steroid or thyroid hormone receptor or a ligand modifying factor and a reporter gene construct responding to a cellular pathway which is induced by a steroid ligand. One skilled in the art can readily envision the species falling within the scope of the claims. The claims involve no vague or unknown materials.

Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, first paragraph.

Rejection of claims 1-2 and 4-5 under 35 U.S.C. § 102(e)

Claims 1-2 and 4-5 stand rejected under 35 U.S.C. § 102(e) as being anticipated by Stuelpnagel et al., (US 2005/0158702 A1) (Stuelpnagel). Applicants respectfully traverse this rejection.

Applicants respectfully submit that the limitation of claim 3 "originating from the human osteoblastic cell line U2-OS" has been moved into claim 1, thereby obviating this rejection.

Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 102(e).

Rejection of claims 1-2 and 4-5 under 35 U.S.C. § 102(b)

Claims 1-2 and 4-5 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Walt et al., (US 6210910 B1) (Walt). Applicants respectfully traverse this rejection.

Applicants respectfully submit that the limitation of claim 3 "originating from the human osteoblastic cell line U2-OS" has been moved into claim 1, thereby obviating this rejection.

Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 102(e).

Rejection of claims 1-2, 4-5, and 11-12 under 35 U.S.C. § 102(e)

Claims 1-2, 4-5, and 11-12 stand rejected under 35 U.S.C. § 102(e) as being anticipated by Giuliano et al., (US 2003/0096322 A1) (Giuliano). Applicants respectfully traverse this rejection.

Applicants respectfully submit that the limitation of claim 3 "originating from the human osteoblastic cell line U2-OS" has been moved into claim 1, thereby obviating this rejection.

Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 102(e).

Rejection of claims 6-8 under 35 U.S.C. § 103(a)

Claims 6-8 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Stuelpnagel et al., (US 2005/0158702 A1) (Stuelpnagel) as applied to claims 1-2 and 4-5 and in view of Wilson et al., (2002, Toxicological Sciences 66:69-81) (Wilson). Applicants respectfully traverse this rejection.

As a threshold matter, Applicants respectfully submit that the Patent Office has failed to establish a prima facie case of obviousness for claims 6 (new claim 35) and 8 over Stuelpnagel and Wilson.

A claimed invention is unpatentable if the differences between it and the prior art "are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art." 35 U.S.C. § 103(a); see Graham v. John Deere Co., 383 U.S. 1, 14 (1966). The ultimate determination of whether an invention is or is not obvious is based on underlying factual inquiries including: (1) determining the scope and content of the prior art; (2) ascertaining the differences between the prior art and the claims at issue; (3) resolving the level of

ordinary skill in the pertinent art; and (4) evaluating evidence of secondary considerations. See Graham, 383 U.S. at 17-18.

The Supreme Court emphasizes that the key of supporting any rejection under 35 U.S.C. §103 is the clear articulation of the reason(s) why the claimed invention would have been obvious. *KSR Int'l Co. v. Teleflex Inc.*, 127 U.S. 1727, 1741 (2007). The Court, quoting *In re Kahn*, stated that "rejections on obviousness cannot be sustained with mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *In re Kahn*, 441, F.3d 977, 988 (Fed. Cir. 2006). Further, if the Office determines there is factual support for rejecting the claimed invention under 35 U.S.C. §103(a), the Office must consider any evidence supporting the patentability of the claimed invention, such as any evidence in the specification.

On page 7 of the Office Action mailed June 22, 2009, the Office asserts that Stuelpnagel teaches a biosensor array of one or more cells or cell lines and relies on the fact that individual cells are biologically or chemically stimulated by the ligands in the cell environment and respond by producing a change in the cell or cellular environment and cells are transformed using variety of vectors and constructs and used to functional assays of various analytes including biomolecules such as steroids. The Office further asserts that Wilson teaches the limitation of plasmids expressing specific hormone receptors and deriving a cell line that could be used as an effective cell-based biosensor for detecting several steroid hormones.

Based on that the Office concludes that although Stuelpnagel does not teach specific component of a steroid receptor or thyroid hormone receptor, it would have been obvious to one skilled in the art to substitute generic biosensor cells in Stuelpnagel live cell biosensor arrays with the biosensor cells equipped with reporter gene expression vectors for effectively detecting steroid hormones and related chemicals in the cellular environment as taught by Wilson and use the modified cell arrays for detecting ligands that affect pathways related to steroid receptors.

In order to support a rejection for obviousness, every element of the claims must be found in the cited art or from common knowledge. In this situation, neither the cited art nor the common knowledge teaches the use of a single cell line allowing effective expression of all steroid receptors in the method for determining the presence of one or more ligands in a sample.

Stuelpnagel does not teach neither the use of relatively small set of cell lines, each expressing a different receptor and originating from a single parent cell line, allowing for a simple and reliable method for determining the presence of one or more ligands in a sample, nor the cell lines that allow discrimination of steroid ligands based on a response, or activity, pattern.

Wilson does not teach human osteoblastic cell line U2-OS comprising an expression plasmid coding for a different steroid or thyroid hormone receptor or a ligand modifying factor and a reporter gene construct responding to a cellular pathway which is induced by a steroid ligand.

Therefore, one of skill in the art would not look to Wilson as teaching a biosensor array of Stuelpnagel. As such, the combination of Stuelpnagel and Wilson do not render *prima facie* obvious claims 6 (new claim 35) and 8 or any of the claims depending therefrom.

The present invention is based on two principles in order to allow for a simple and reliable method for determining the presence of one or more ligands in a sample (p. 3, ll. 22-24 of the specification as originally filed). First the identification of a single cell line allowing effective expression of all steroid receptors (p. 5, ll. 1-2, p. 11, ll. 1-10 of the specification as originally filed). The use of a single parent cell line allows for a better comparison between the individual cell lines in the array and the detection of non-specific effects (p. 4, ll. 31-33 of the specification as originally filed). Second, the finding that with a limited set of cell lines, discrimination of different steroid ligands can be improved (p. 17, ll. 17-19, p. 18, ll. 1-36 of the specification as originally filed).

These results and findings are not predictable from the cited art and are an independent reason as to why the present claims are non-obvious.

For all of the foregoing reasons, Applicants respectfully submit that this obviousness rejection should be withdrawn because (a) the Office has failed to make a *prima facie* case of obviousness based on Stuelpnagel in view of Wilson and (b) the results observed and presented by the Applicants were not predictable.

Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a).

Rejection of claims 3, 6-8, and 10 under 35 U.S.C. § 103(a)

Claims 3, 6-8, and 10 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Stuelpnagel et al., (US 2005/0158702 A1) (Stuelpnagel) as applied to claims 1-2 and 4-5 and in view of Quaedackers et al. (2001, Endocrinology 142:1156-1166) (Quaedackers). Applicants respectfully traverse this rejection.

The Office based the rejection on teachings of Stuelpnagel as discussed in the previous section. On page 9 of the Office Action mailed June 22, 2009, the Office further asserted that Quaedackers teaches the limitation of plasmids expressing specific hormone receptors under the control of the hormone responsive elements.

Based on that, the Office concludes that although Stuelpnagel does not teach specific component of a steroid hormone receptor or thyroid hormone receptor it would have been obvious for one of ordinary skill in the art to substitute generic biosensor cells in Stuelpnagel live cell-based biosensor with Osteoblastic U2-OS cell lines equipped with reporter gene expression under control of hormone responsive elements as taught by Quaedackers.

The Office's reliance on Stuelpnagel is deficient for the reasons provided above, and Quaedackers does not compensate for these deficiencies.

The present invention teaches the use of at least two U2-OS cell lines expressing a different hormone receptor and comprising a reporter gene construct cell lines in a method for determining the presence of one or more steroid hormones in a sample.

In contrast Quaedackers teaches cell lines that provide almost identical response to progesterone (progestin), MPA (progestin), androstenedione (adrenal androgen), testosterone (androgen), R1881 (androgen), and dexamethason (corticosteroid) thereby allowing no discrimination between these steroid hormones. Furthermore, Quaedackers does not teach a single cell line comprising the estrogen alpha receptor (ER-alpha) that also responds, besides to estrogens, to other steroid ligands such as progestins, adrenal androgens and corticosteroids

Therefore, one of skill in the art would not use the single cell line of Quaedackers in a biosensor array of Stuelpnagel to arrive at the claimed invention. As such, the combination of Stuelpnagel and Quaedackers do not render *prima facie* obvious claims 3 (new claims 27-28), 6 (new claim 35), 7-8, and 10 or any of the claims depending therefrom.

Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a).

Double patenting warning

Applicants respectfully submit that as amended claims 4 (new claims 29 and 30) and 5 (new claims 31-34) are not substantial duplicates of claim 1.

Rejoinder of withdrawn claims

Claims 7, 9, and 26-30) are generic/linking claims. Accordingly, pursuant to MPEP 821.04, Applicants request reconsideration of the restriction requirement and rejoinder of claims 18-24 upon allowance of the generic/linking claims.

In light of the all above arguments, Applicants respectfully request reconsideration and withdrawal of the rejections of the pending claims. If the Examiner believes it to be helpful, he is invited to contact the undersigned representative by telephone at (312) 913-0001.

Respectfully submitted,

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